

## **REMARKS**

The Office Action dated August 3, 2007 has been carefully considered. Applicants believe that the present Amendment, taken with the accompanying remarks, is sufficient to establish the compliance of the application with statutory mandates under 35 U.S.C. § 112. Applicants respectfully submit that the Examiner has misinterpreted and overlooked certain significant teachings in the specification and submit clarifications establishing the sufficiency of the disclosure. Claim 1 is amended merely to spell out the long form of "OprF" in accordance with the specification, and to delete the terms "a" and "substantially." As it is believed that the Amendment does not raise an issue of new matter, entry is believed in order and is therefore respectfully requested.

Claims 1-10 remain pending and claims 1, 2 and 9 are currently subject to examination.

### **Objection to the Drawings**

An objection to the drawings is maintained "for reasons of record." Applicants, note however, that the original objection related to the lack of readability of the gel data set forth in Figure 4. In a response dated November 3, 2006, Applicants submitted a revised Figure 4 that was drawn by an expert draftsman and cannot reasonably be said to be lacking clarity. On January 4, 2007, Applicants re-submitted the replacement drawing sheet in response to a Notice of Noncompliance indicating that the original replacement sheet was not properly labeled as such. The Examiner has not acknowledged this submission nor its effect on the objection and Applicants are concerned that it is not properly before the Examiner. Applicants respectfully request clarification as to the status of entry of the replacement drawing into the application. In the alternative, if the replacement sheet has been inspected but remains objected to for the same initial reasons, Applicants respectfully request a more detailed explanation as to the deficiencies so that these may be submitted to the patent draftsman who prepared the replacement sheet. Applicants submit that the gel results depicted on the replacement drawing are as clear as can possibly be rendered and respectfully submit that if properly considered, the objection is overcome.

### **Election/Restriction Requirement**

The Examiner asserts that restriction and withdrawal is proper with respect to newly added claims 9 and 10, as being drawn to non-elected inventions. Applicants withdraw claim 10 without traverse, but submit that the Examiner misconstrues claim 9 by improperly reading an element into the claim that is not there. As drafted, the "detecting" of claim 9 refers back to the "detecting" step of claim 1, that is, "detecting the presence or absence of ..." According to claim 9, the detecting comprises detecting up-regulated expression of OprF. Contrary to the parenthetical assertion by the Examiner, this does not demand that mRNA be detected, and relies on detection of the protein that is the expression product of any up-regulated mRNA. According to claim 1, a practitioner is detecting a presence or absence of *Pseudomonas aeruginosa* outer membrane protein (OprF) in a sample from an individual. Dependent claim 9 properly narrows this claim because detection of up-regulated expression of OprF, or an increase in OprF expression, is a detection of presence. The claim does not require the practitioner to detect "up-regulation," per se, but to detect an increase in expression, which may be via detecting the protein or the mRNA in theory, but claim 1 already limits "detecting" to the protein. Claim 9 is therefore directed properly to a dependent embodiment of claim 1 which is within the scope of claim 1, and cannot be said to constitute an independent invention distinct therefrom.

Hence, Applicants submit that claim 9 should properly be examined with claims 1 and 2 in this application as being directed to a dependent embodiment of the invention defined by independent claim 1. Reconsideration is therefore respectfully requested.

### **35 U.S.C. § 112, Enablement**

The rejection of claims 1-2 under 35 U.S.C. § 112, first paragraph, for lack of enablement by the specification, is maintained "for reasons of record." Specifically, the Examiner asserts that the specification enables methods for detecting the specified OprF, it does not enable methods for assessing cystic fibrosis disease based on this detection, and does not enable "determination of whether a mucous lining in an airway of the individual is substantially anaerobic."

In particular, the Examiner asserts that "the specification is enabling for methods of detecting a *Pseudomonas aeruginosa* infection by the detection of its OprF but does not reasonably provide enablement for methods for assessing cystic fibrosis disease based on the presence or absence of any *Pseudomonas aeruginosa* outer membrane protein generally, or OprF specifically; and the determination of whether a mucous lining in an airway of the individual is substantially anaerobic."

In the Examiner's notes of guidance provided in the specification (see page 5 of August 3, 2007 Office Action), the Examiner cites to disclosure of the prevalence of *P. aeruginosa* infection in CF patients, the harvesting of OprF from CF patient lungs, the observed worsening of CF disease when *P. aeruginosa* converts to mucoid, alginate-overproducing form which is coupled to anaerobic growth and an increase in OprF, the asserted disclosure that "the mucous lining of airways is anaerobic (especially in CF patients), and the definition of "assessment" as set forth in the specification. The Examiner then asserts that the specification "is silent" on "how the goals are to be accomplished using a single time point detection of a protein" and "what role the 'determination' of the anaerobicity of the mucous lining (which is disclosed in the specification as always being anaerobic) plays in said assessment." This rejection is traversed and reconsideration is respectfully requested.

Independent claim 1 is directed to a method for Cystic Fibrosis (CF) disease assessment in an individual, the method comprising: (a) detecting the presence or absence of *Pseudomonas aeruginosa* outer membrane protein F (OprF) in a sample from an individual; (b) making a determination of whether a mucous lining in an airway of the individual is anaerobic, and (c) assessing the disease of the individual accordingly.

First, Applicants point out that the Examiner's contention regarding the use of the article "a" in claim 1 is mooted in view of the deletion of the article. Applicants note, however, that the original use was adopted merely to conform to standard article usage in claim drafting in the absence of an antecedent recitation.

With respect to the uniqueness of the specified pathogen, attached hereto as exhibit A is a scholarly article that discusses OprF and evidences that a person of ordinary skill in the art would recognize that the phrase "*Pseudomonas aeruginosa* outer membrane protein F (OprF)" uniquely describes the disclosed and recited species. Applicants note that the substance of the article is irrelevant to the patentability of the claims, but that the article is being submitted to evidence Applicants' contention that the scope of "OprF" or, specifically, "*a Pseudomonas aeruginosa* outer membrane protein F (OprF)" as recited in claim 1, is clearly defined.

Applicants respectfully submit that the Examiner misconstrued certain disclosure in the specification, and missed other significant disclosure, in his enablement analysis. With respect to this misconstruction (see double underlined portion of quote by Examiner, above), Applicants submit that the Examiner's interpretation of text on page 11 is simply not a reasonable interpretation. This paragraph (lines 1-3) must be taken out of context in order to conclude it means that the mucous lining in airways is always anaerobic, as this simply is not

supported in context. The paragraphs prior to this text discuss the transition of mucous from aerobic to anaerobic with progression of the disease. The cited text states that the inventors discovered that increased OprF expression is evidence that that mucous lining of airways of a CF patient is anaerobic. In other words, it has undergone the transition that indicates progression of the disease to a chronic state. The text following this passage makes this clear, as it discloses that certain "front-line" antibiotics useful for treating CF become ineffective in an anaerobic environment. Knowing when an anaerobic condition evolves is therefore important to efficacy of treatment. Contrary to the representation by the Examiner, the specification *never* teaches that the mucous lining in airways is "always" anaerobic. Indeed, it is the fact that the oxygen conditions in the airway mucosa transition that underpins the presently inventive methods, as detection of *Pseudomonas aeruginosa* OprF in the mucosal lining of the airway leads to the determination that the mucosal lining is anaerobic, which renders assessment of the CF disease possible.

The Examiner asks - what role would such a determination play in assessment? As noted by the Examiner, the definition set forth in the specification for assessment includes, inter alia, tailoring a treatment regimen. The remainder of the disclosure on page 11 provides one exemplary embodiment - where a course of antibiotic is found to be ineffective under anaerobic conditions, treatment may be accordingly tailored to one that is effective under anaerobic conditions.

Further, Applicants respectfully submit that the Examiner has overlooked portions of the specification and is simply wrong when he asserts that the specification is silent as to "how the goals [of the claim] are to be accomplished using a single time point detection of a protein." Applicants point specifically to disclosure found on pages 23-24 and Table 1 on pages 25-26. As noted, 31 protein spots were analyzed under aerobic and anaerobic conditions (see last column of Table 1 and page 23, lines 12-23). Significantly, of the 31 proteins analyzed, only two were found exclusively in anaerobic biofilms - L9 and OprF. Hence, it is clear that detection of OprF in mucosal airways indicates the emergence of anaerobic conditions and progression of CF lung disease to a chronic state.

Since the scope of claim 1 is limited to the very specific OprF recited, and the step of making a determination of whether a mucous lining in an airway of the individual is substantially anaerobic, based on this, is fully enabled, and the nexus between this determination and assessment of the disease is established as noted, Applicants respectfully submit that the disclosure of the instant specification enables the full scope of the inventive

methods defined by claims 1, 2 and 9 and the rejection under 35 U.S.C. § 112 for lack of enablement has been overcome. Reconsideration is respectfully requested.

### **35 U.S.C. § 112, Written Description**

The rejection of claims 1-2 under 35 U.S.C. § 112, first paragraph, for failing to comply with the written description requirement is maintained "for reasons of record." On the record, the Examiner asserts that the claims are drawn to methods of assessing CF disease by detecting the presence or absence of outer membrane protein in a sample where "assessing" is defined according to the specification to include a number of activities, and that the instant claims therefore claim "all outer membrane proteins of any cell type or organism whereas the specification only discloses the prevalence of *Pseudomonas aeruginosa* infections among CF patients," and "fails to describe any other outer membrane protein that is either directly or indirectly associated with CF."

In response to Applicants' prior arguments, the Examiner argues that use of the article "a" suggests that there is more than one outer membrane protein being claimed, and asserts that the recitation of the abbreviated OprF is confusing. This rejection is traversed and reconsideration is respectfully requested.

As presently amended, independent claim 1 is directed to a method for Cystic Fibrosis (CF) disease assessment in an individual, the method comprising: (a) detecting the presence or absence of *Pseudomonas aeruginosa* outer membrane protein F (OprF) in a sample from an individual; (b) making a determination of whether a mucous lining in an airway of the individual is anaerobic, and (c) assessing the disease of the individual accordingly.

First, the issue with respect to use of the article "a" is mooted since Applicants have deleted the term. Second, Applicants submit that the amendment to add the "F" designation to the outer membrane eliminates the potential for confusion regarding meaning of the abbreviated form "OprF." Applicants submit that a person of ordinary skill in the art would be absolutely clear as to the identity of the species of pathogen as defined by the language of claim 1, and that the scope of the claim is commensurate with the support in the written description. Hence, the rejection of claims 1 and 2 under 35 U.S.C. § 112 for lack of written description has been overcome. Reconsideration is respectfully requested.

### **35 U.S.C. § 112, Indefiniteness**

The rejection of claims 1 and 2 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite due to the "confusing" use of the abbreviation "OprF," is maintained.

Specifically, the Examiner asserts that claim 1 is rendered vague and indefinite by the parenthetical use of the term "OprF" because it is unclear whether this term is meant to be an abbreviation for outer membrane proteins generally or is referring to the porin F protein of *Pseudomonas aeruginosa*. This rejection is traversed and reconsideration is respectfully requested.

As amended, independent claim 1 recites "*Pseudomonas aeruginosa* outer membrane protein F (OprF)," which fully expresses the expanded form of the abbreviated "OprF," and specifies it further by species. Hence, Applicants submit that the instant claim, as amended, makes the identity and scope of the term "OprF" readily ascertainable by a person of ordinary skill in the art. Reconsideration is respectfully requested.

**Claims 1-2** are further asserted to be indefinite due to the use of the phrase "substantially anaerobic," since the term is not defined in the specification and it would be unclear what level of oxygen can be present wherein (the mucous lining is still considered "substantially anaerobic." This rejection is traversed and reconsideration is respectfully requested. As amended, the term "substantially" is deleted from the claim which obviates the issue. Applicants must point out however, that deletion is not meant to imply that a 100% determination is necessary, as a strict boundary does not exist. Reconsideration is respectfully requested.

**Claims 1-2** are also asserted indefinite for use of the phrase "assessing the disease of the individual accordingly." Specifically, the Examiner states that it is "unclear on what said 'assessment' is based," and asks "How is the result of the 'determination' of step (b) utilized?" This rejection is traversed and reconsideration is respectfully requested.

Applicants submit that it is clear from the teachings in the specification that assessment is "based on" a determination of whether the mucosa lining of the airway is anaerobic. Applicants provide the following non-limiting and disclosed example of how the result of the determination step is utilized: the specification teaches that the efficacy of certain front-line antibiotics is reduced under anaerobic conditions (page 11, lines 8-11). The term "assessment" is clearly defined in the instant specification on page 12, lines 20-22, bridging to page 13, lines 1-2. Although this definition may differ somewhat that the ordinary meaning of the word, it is clear that all the listed examples utilize a determination of whether the mucosal lining of the airway is anaerobic, as all examples are underpinned by the teaching that such a determination is indicative of a progression of the disease toward chronic status (see, e.g. Figure 5 comparing serum from normal patients, normal individuals with *P. aeruginosa* pneumonia, CF patients with no *P. aeruginosa*, and chronically infected CF

patients; see also page 11, lines 6-9), such that prognosis, monitoring and intervening may be indicated in accordance. As already noted, a determination may be indicative of the value of certain treatment regimens enabling prediction of response to a therapy regimen or tailoring response to a therapy regimen. Applicants submit, therefore, that the answers to the Examiner's queries are set forth clearly in the specification. Reconsideration is respectfully requested.

### **35 U.S.C. § 112, first paragraph, new matter**

Claim 1-2 are rejected under 35 U.S.C. § 112, first paragraph, as assertedly containing new subject matter. Specifically, the Examiner notes Applicants' amendment to claim 1 to add the recitation "making a determination of whether a mucous lining in an airway of the individual is substantially anaerobic, and (c) assessing the disease of the individual accordingly..." The Examiner asserts that this phrase does not appear in the specification or in the original claims as filed. The Examiner asserts that the disclosure at page 11, lines 6-16 "merely is a disclosure of the fact that the mucous lining of airways is anaerobic," which does not provide support for a step where anaerobicity of the mucous lining is determined. This rejection is traversed and reconsideration is respectfully requested.

Applicants respectfully submit that the Examiner's misunderstanding of this text, as set forth supra, underpins his conclusion that the added step constitutes new matter. The text cited by Applicants supports the actual language used to define the step. Support for the actual step, however, comes from the text beginning on page 10 and continuing through page 11, taken with the data reported in Table 1 that illustrates the basis for the instant methods, i.e. that only 2/31 proteins were found solely in anaerobic biofilms. This characteristic make it an ideal assessment tool, as noted by the specification.

First, however, the Examiner must understand that the text on page 11 does *not* stand for the proposition that the mucosa lining of airways is always anaerobic and the specification does not teach this. In fact, as would be understood by a person of ordinary skill in the art, and as noted in the specification, under normal aerobic conditions in normal lungs, and under static aerobic conditions characteristic of pre-chronic CF lung disease, mucoid bacteria exist or revert to a form that is disposed of by the bodies immune defense system (see, e.g. page 11, lines 1-5). As lung disease in CF patients progresses, bacterial infections begin to consume oxygen and provide an environment suitable for emergence of anaerobic biofilms

that are not as amenable to attack by the body's defenses or to treatment with antibiotics (see page 8, lines 10-14, page 11, lines 8-11, and page 8, lines 15-20).

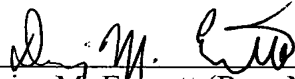
The method step of detecting the presence or absence of OprF is based on these and other discoveries by the inventors. The Examiner previously suggested that a nexus must exist between the detection and the assessment. Applicants argue that it impliedly does, based on the teachings in the specification, that is, presence of OprF indicates presence of anaerobic biofilms, which, as taught in the specification, signals chronic lung infection. The step of determining whether the mucosa lining of the airway is substantially aerobic is the express nexus from detecting to assessment, and the cited disclosure on page 11 makes this clear, taken with recognition of the data set forth in Table 1. The text on page 11 notes that the inventors discovered that detection of OprF provides evidence that the mucous lining of the airways of a CF patient are anaerobic. The clause "especially in chronically infected CF patients" is admittedly ill-placed, but is meant to underscore that this discovery is especially salient evidence of a chronic infection in a CF patient (see also, page 13, lines 22-24, bridging to page 14, lines 1-3).

Since it is fully supported by disclosure in the specification, albeit not word-for-word, Applicants submit that the language added to claim 1 does not constitute new matter and respectfully request reconsideration of this rejection.

### **Conclusion**

It is believed that the above is a complete and comprehensive response to the rejections of claims 1-2 and 9 under 35 U.S.C. §§ 112, first and second paragraphs, as asserted in the August 3, 2007 Office Action, and therefore places the present application in condition for allowance. Reconsideration and an early allowance are respectfully requested.

Respectfully submitted,

  
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